UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/068,725	02/06/2002	Wayne Kindsvogel	01-04	8714

10117 7590 04/10/2007

ZYMOGENETICS, INC.
INTELLECTUAL PROPERTY DEPARTMENT
1201 EASTLAKE AVENUE EAST
SEATTLE, WA 98102-3702

EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	**PAPER NUMBER**
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

A

Office Action Summary	Application No.	Applicant(s)	
	10/068,725	KINDSVOGEL, WAYNE	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10 and 25-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10 and 25-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 9 and 11-24 are canceled.

Claims 1, 10 and 25-29 have been amended.

Claims 30-32 have been added.

2. Claims 1-8, 10 and 25-32 are pending and under consideration.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Rejections.

Rejections Withdrawn

5. The rejection of claims 1-8, 10 and 25-29 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation "at an eptiope within a polypeptide consisting of at least one of amino acids..." in claim 1 is withdrawn in view of the amendments to the claims.

6. The rejection of claims 1-8, 10, and 25-27 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as introducing new matter is withdrawn in view of applicants' arguments and the amendments to the claims.

Response to Arguments

7. The rejection of claims 28-29 and now applied to newly added claims 31-32 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as introducing new matter is maintained. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The response filed 1/19/2007 states that while applicant disagrees, the claims have been amended to speed prosecution. This has been fully considered but is not found persuasive. The claims still recite that binding to TACI is within amino acids 39 to

50, or 78 to 91 of SEQ ID NO:4. It is reiterated that the as filed disclosure at pg. 4, lines 22-26 discloses that the anti-BCMA-TACI antibody components can bind a polypeptide having the amino acid sequence of amino acids 39 to 50 of SEQ ID NO:4 or a polypeptide having the amino acid sequence of amino acids 78 to 91 of SEQ ID NO:4. Thus, the disclosure only provides adequate written support for the anti-BCMA-TACI antibody components that binds TACI, since TACI is a polypeptide "having" the amino acid sequence of amino acids 39 to 50 of SEQ ID NO:4 or amino acids 78 to 91 of SEQ ID NO:4. See MPEP 2111.03. The specification does not provide any direction or guidance to the to provide adequate written support for antibodies specific to the recited epiotpes within amino acids 39 to 50 of SEQ ID NO:4 or within amino acids 78 to 91 of SEQ ID NO:4. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See *In re Smith* 173 USPQ 679, 683 (CCPA 1972). Applicant is required to provide sufficient written support for the limitations recited in newly added claims 28-29 in the specification or claims, as-filed, or remove these limitations from the claims in response to this Office Action. For these reasons there is also insufficient written support for the claimed method wherein the anti-BCMA-TACI antibody components that bind BCMA within amino acids 13 to 27 of SEQ ID NO:2 and the binding to TACI is within amino acids 39 to 50, or 78 to 91 of SEQ ID NO:4. It is noted that the as filed specification appears to provide adequate written support for the limitation wherein the anti-BCMA-TACI antibody components bind BCMA within amino acids 13 to 27 of SEQ ID NO:2 (e.g., see pg. 16).

8. Claims 1-8 and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Theill et al (US Patent 6,774,106 B2, priority to 5/12/2000) in view of Gross et al (WO 00/40716, 7/13/2000) is maintained.

The response filed 1/19/2007 states that Gross et al do not teach the specific fragment (amino acids 1 to 54) nor subfragment (amino acids 13 to 27) of BCMA presently claimed and it would not have been obvious to one of ordinary skill that using a larger or smaller subfragment of this molecule as an epitope would result in an

antibody that would bind both TACI and BCMA. Applicant notes that the presently claimed antibodies are an unexpected result of screening antibodies that bound well to the TACI molecule for ability to bind BCMA in view that the cysteine rich repeats of the extracellular domains of BCMA and TACI share minimal homology, only on the order of 32.3% identity (see attached FASTA printout in the reply filed 1/19/07). Thus, based on the low homology, one of ordinary skill in the art would not have been led or expected to find an antibody that binds both BCMA and TACI. Applicant arguments have been fully considered but are not found persuasive. While the examiner agrees that based on the low homology between the cysteine rich repeats of the extracellular domains of BCMA and TACI, it would not have been obvious to produce a monoclonal antibody that binds both BCMA and TACI within the claimed cysteine rich repeats of the extracellular domains. However, it is noted that the features upon which applicant relies (i.e., monoclonal antibody that binds both BCMA and TACI) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, Theill teach that the antibody that binds both BCMA and TACI for inhibiting the proliferation of tumor cells can be a bispecific antibody or heteroantibody having two different antigen binding sites and Theill teach the cysteine rich repeats in the extracellular domains of both BCMA and TACI (see Figs. 11-12). Applicant has not provided any objective evidence that one of ordinary skill in the art would not have a reasonable expectation of success from the teachings in the prior art of obtaining a bispecific antibody that binds the cysteine rich repeat in the extracellular domains of both BCMA and TACI, particularly where the two antigen-binding sites are produced separately against the cysteine rich repeat of BCMA and the cysteine rich repeat of TACI. Applicant is reminded that the arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and

allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant.

Therefore, for these reasons and those already of record, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references and the rejection is maintained.

New Grounds of Objections/Rejections

9. Claims 26-27 are objected to in the recitation "wherein the binding to TACI within amino acids...", which is grammatically incorrect. Consider amending the claims to recite wherein the binding to TACI is within amino acids...".

Appropriate correction is required.

10. Claims 1-8, 10 and 25-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in the recitation "antibody component" as the exact meaning of the term is unclear. The specification defines the term "antibody component" to include both an entire antibody and an antibody fragment and that antibody components include polyclonal antibodies, murine monoclonal antibodies, humanized antibodies derived from murine monoclonal antibodies, chimeric antibodies, human monoclonal antibodies, and the like (see pg. 14, lines 30-31 and pg. 4, lines 27-29). It is unclear what "antibody component" is contemplated by "and the like", the specification does not define what is meant by "and the like", the terminology embraces antibody variants comprising amino acid substitutions, deletions, insertions, chemically derivatized antibodies, mimetics, ect. There is no way for one skilled in the art to ascertain the requisite degree, direction or endpoint of an "antibody component" as defined by "and the like" and as such one of skill in the art would not be reasonably apprised of the metes and bounds of the claimed antibody components.

11. Claims 1-8, 10 and 25-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting the proliferation of tumor cells comprising endogenous B-cell maturation antigen (BCMA) or transmembrane activator and calcium-modulator and cyclophilin ligand-interactor (TACI) comprising administering a composition comprising dual reactive BCMA-TACI monoclonal antibody, 255.7, (assuming the enablement of monoclonal antibody 255.7, i.e., biological deposit), or administering a composition comprising a bispecific BCMA-TACI antibody, wherein binding to BCMA is within amino acids 1 to 54 or 13 to 27 of SEQ ID NO:2 and the binding to TACI is within amino acids 30 to 67 or 68 to 154 of SEQ ID NO:4 and wherein the method further comprises the administration of an additional antibody that binds within amino acids 110 to 118 or 105 to 166 of SEQ ID NO:4, does not reasonably provide enablement for a method for inhibiting the proliferation of tumor cells comprising endogenous BCMA or TACI comprising administering a composition comprising an antibody component that binds BCMA and TACI, wherein binding to BCMA is within amino acids 1 to 54 or 13 to 27 of SEQ ID NO:2 and the binding to TACI is within amino acids 30 to 67 or 68 to 154 of SEQ ID NO:4, and wherein the method further comprises the administration of an additional antibody component that binds within amino acids 110 to 118 or 105 to 166 of SEQ ID NO:4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are drawn to a method for inhibiting the proliferation of tumor cells comprising endogenous BCMA or TACI comprising administering a composition comprising an antibody component that binds BCMA and TACI, wherein binding to BCMA is within amino acids 1 to 54 or 13 to 27 of SEQ ID NO:2 and the binding to TACI is within amino acids 30 to 67 or 68 to 154 of SEQ ID NO:4. Further, the claimed method comprises administration of an additional antibody component that binds within amino acids 110 to 118, or 105 to 166 of SEQ ID NO:4. Thus, the claims are drawn to a genus of "antibody components" that bind both BCMA and TACI at the recited BCMA and TACI epitopes for inhibiting the proliferation of tumor cells.

The specification discloses that "antibody components" include polyclonal, murine, humanized, chimeric, human monoclonal andtibodies and the like as well as antibody fragments including F(ab')2, F(ab)2, Fab', Fab, Fv, scFv and minimal recognition units (see pp. 4-5 and 14-15). The specification teaches the production of murine monoclonal antibodies prepared against a polypeptide representing a fragment of the BCMA extracellular domain, wherein a particular monoclonal antibody, monoclonal antibody 255.7, bound both BCMA and TACI, an unexpected finding in view of the low level of amino acid sequence identity between BCMA and TACI (see pg. 3). The specification teaches that monoclonal antibody 255.7 recognizes a structure within the cysteine-rich regions of both BCMA and TACI, blocks the binding of ZTNF4 to either BCMA or TACI and inhibits tumor growth (see pp. 3-4 and Examples). The specification does not teach the genus of "antibody components" that bind both BCMA and TACI, including monoclonal antibodies other than monoclonal antibody 255.7 or "antibody components" that contain fewer than all six CDRs, three from the heavy chain and three from the light chain and do not bind antigen as encompassed by "and the like" and "minimal recognition units". There are no working examples of "antibody components" that bind both BCMA and TACI, including monoclonal antibodies other than monoclonal antibody 255.7 or "antibody components" that contain fewer than all six CDRs, three from the heavy chain and three from the light chain and do not bind antigen. The scope of the claims must bear a reasonable correlation with the scope of enablement. See *In re Fisher*, 166 USPQ 19 24 (CCPA 1970).

The state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of antibodies routinely requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, 3rd Edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79:1979-1983, 1982). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Coleman P. M. (Research in Immunology, 145:33-36, 1994) teaches that even a very conservative substitution may abolish binding or may have very little effect on the binding affinity (see pg. 35, top of left column and pg. 33, right column). It is unlikely that "antibody components" that contain fewer than all six CDRs, three from the heavy chain and three from the light chain as encompassed by "and the like" and "minimal recognition units" have the requisite BCMA and TACI binding function. There is no guidance or direction to assist the skilled artisan in making and using "antibody components" that are like an antibody and contain fewer than all six CDRs, three from the heavy chain and three from the light chain and bind BCMA and TACI. Further, the prior art also recognized that even minor changes within the epitope may dramatically affect antibody binding. For example, Lederman et al (Molecular Immunology 28:1171-

1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Li et al (Proc. Natl. Acad. Sci. USA 77:3211-3214, 1980) disclose that dissociation of immunoreactivity from other activities when constructing analogs (see entire document). The art Theill et al (U.S. Patent 6,774,106 B2; cited on PTO-892 mailed 7/20/06) teaches that there is significantly low homology between the cysteine rich extracellular regions of BCMA and TACI. Thus, one of ordinary skill in the art could not predictably extrapolate the unexpected BCMA-TACI binding property of monoclonal antibody 255.7 to the genus of monoclonal antibodies (i.e., "antibody components") that bind both BCMA and TACI. It is unlikely that a monoclonal antibody produced against a polypeptide representing a fragment of the BCMA extracellular domain would also bind TACI. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. One of skill in the art would neither expect nor predict the appropriate functioning of the antibodies as broadly as is claimed.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Paul W. E., Rudikoff et al, Coleman, P. M., Lederman et al, Li et al and Theill et al the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed genus of antibody components, including monoclonal antibodies that bind BCMA and TACI, "and the like" (i.e., antibody variants), and minimal recognition units having fewer than all six CDRs that bind BCMA and TACI for inhibiting the proliferation of tumor cells, with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed "antibody components" and absent working examples providing evidence which is reasonably

predictive that the claimed "antibody components" bind BCMA and TACI, commensurate in scope with the claimed invention.

Applicant is advised that an amendment to the claims directed to dual reactive BCMA-TACI monoclonal antibody 255.7 would require that the antibody is (1) known and readily available to the public; or (2) reproducible from the written description in order to satisfy the enablement for monoclonal antibody 255.7.

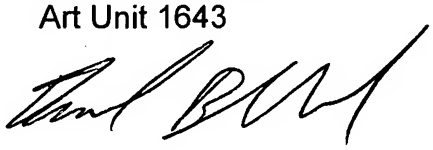
12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Blanchard
Patent Examiner
Art Unit 1643



DB
April 2, 2007